DEC 2 1 2005

TRW 1646

Docket No: 13140
(01017/40451C)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Brockhaus et al.

Application No.: 08/444,791 Art Unit: 1646

Filed: May 19, 1995 Examiner: R. Schwadron, Ph.D

For: HUMAN TNF RECEPTOR

TRANSMITTAL OF SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

The following information and attached documents are being brought to the attention of the U.S. Patent and Trademark Office pursuant to the duty of disclosure under 37 C.F.R. § 1.56. Since this statement is filed after an Office Action on the merits and before a final action, the Commissioner is hereby authorized to charge a fee of $180 to Deposit Account No. 13-2855, as required by 37 C.F.R. § 1.17(p). The Commissioner is also hereby authorized to charge any additional fees that may be required or credit any overpayment to Deposit Account No. 13-2855.

Dated: December 20, 2005

Respectfully submitted,

By Li-Hsien Rin-Laures

Li-Hsien Rin-Laures
Registration No.: 33,547
MARSHALL, GERSTEIN & BORUN LLP
233 S. Wacker Drive, Suite 6300
Sears Tower
Chicago, Illinois 60606-6357
(312) 474-6300
Attorney for Applicant

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Brockhaus et al.

Application No.: 08/444,791

Art Unit: 1644

Filed: May 19, 1995

Examiner: R. Schwadron, Ph.D

For: HUMAN TNF RECEPTOR

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

This submission is not an admission that the submitted information is material to the patentability of the pending claims. 37 C.F.R. § 1.97(h).

Attached to this Information Disclosure Statement are Exhibits A through M. These exhibits are copies of documents that were kept in the normal course of business at Immunex Corporation (now Amgen Inc.). For Exhibits A-E, H, and L, information that is unrelated to TNF receptor has been redacted. Exhibits B, F, I, K, L and M were shown to Examiner Ronald Schwadron during a personal interview on September 20, 2005. Additional investigation produced other documents that are also included herewith. The events described in these documents are set out below and in the attached declaration under 37 CFR § 1.132 of Terri Davis-Smith. All documents submitted are listed in chronological order in attached Table 1.

In reviewing Exhibits A-M, the Examiner is requested to note that, under 35 U.S.C. §102(g), another's invention constitutes prior art only if "before [the applicant's] invention thereof, the invention was made in this country by another inventor who had not abandoned, suppressed, or concealed it." Invention under 102(g) requires both conception and reduction to practice. Conception requires that the inventor appreciate that which he has invented and that the inventor has an objective basis for doing so. *Invitrogen v. Clontech*, 2005 WL 3078495 (Fed. Cir. Nov. 18, 2005). Where the invention is made abroad, all elements of the invention (i.e. conception and reduction to practice) must be introduced, and in some cases, performed, in this country.

In the attached exhibits, three independent experimental efforts are documented. The first involves a collaboration between Immunex and Behringwerke AG and is documented in Exhibits A, B, D- I, and K-M and explained below. The second is an unsuccessful effort at Immunex to express active fusion proteins in yeast. The third involves work performed at the University of Texas.

1) Immunex/Behringwerke Collaboration

On October 24, 1989, Immunex scientists met with Dr. Leander Lauffer of Behringwerke in Seattle at Immunex, and it was agreed that Behringwerke would engineer soluble forms of various receptors (including the TNF receptor, "TNFR") into Fc fusion proteins. **Exhibit A.**

On February 26, 1990, Dr. David Urdal, Vice President and Director of Development at Immunex, sent to Dr. Lauffer of Behringwerke in Germany, a mammalian expression vector, called "CAVNOT Hu TNFR-1," comprising cDNA encoding the human p75 TNF receptor, which Immunex had cloned. **Exhibit B.**

On May 21, 1990, Dr. Lauffer wrote to Dr. Urdal about two receptor Fc fusion proteins (neither of which was a TNFR Fc fusion) and gave the sequence of an Fc-encoding portion of a vector in use at Behringwerke and restriction sites for fusions with receptor sequences. **Exhibit D.** On the sequence is indicated a BamHI site "used for fusions," as well as positions of "any receptor sequence" and a "linker." The start points of the hinge, CH2, and CH3 regions are also indicated.

During a June 25, 1990 internal meeting at Immunex, it was announced that a supernatant from COS cells transfected with DNA encoding a sTNFR-Fc had been sent by Behringwerke (**Exhibit E**). COS cells are a mammalian (monkey) cell line.

On July 11, 1990, a sample labeled as a TNFR-Fc COS supernatant was tested for the ability to inhibit binding of radioactive TNF to U937 cells. This experiment is documented in attached **Exhibit F**, which is explained in the attached declaration of Terri Davis-Smith, who performed the experiment.

On July 20, 1990, Dr. Deeley of Immunex wrote a letter (**Exhibit G**) to Dr. Lauffer reporting the results documented in Exhibit F. The letter states, "The supernatant does contain some binding inhibition activity relative to controls. . . In our experience the amount of binding

inhibition is believable and comparable to the amount seen in Cos cell supernatants expressing our soluble TNFR construct. When we concentrate (8-10 fold) supes containing our construct, we obtain 50-70% binding inhibition. We are currently concentrating your supe and will perform the assay. I will send you that data in approximately one week."

On July 23, 1990, the results documented in Exhibit F were reported at an internal meeting at Immunex. **Exhibit H**. According to the meeting minutes, "Single point assay gave approximately 15% inhibition [sic] above background suggesting a low level of the receptor (approximately equal to that found for unconcentrated COS cell supernatents [sic] with Immunex's sTNFr?)."

On August 8, 1990, Behringwerke wrote a letter to Immunex (**Exhibit I**) stating that Behringwerke was willing to send cell lines expressing the proteins but that they would not send vectors encoding the fusion proteins. The letter states: "We are at the moment in the process of characterizing this protein. As soon as we have finished our initial studies concerning its structural and functional properties, we will forward a suitable cell line to you. . . We do not feel able to send you these plasmids, as we are applying for patent protection for various applications. At the present time, we would prefer [to] continue with our present working arrangement, in which Behring performs [the] construction and initial characterization of all receptor/Fc fusion proteins and Immunex continues to do the corresponding experiments with the soluble receptors."

On September 10, 1990, the U.S. priority application of the present application (U.S. Application No. 07/580,013) was filed. Exhibits K-M are dated subsequent to the filing date of this U.S. priority application.

On September 13, 1990, Berhingwerke's U.S. App. No. 08/478,995 was filed (Document No. A11 on the 1449 form filed March 25, 2005). This application generally discusses Fc fusions of various receptors, including TNF receptors, and was co-owned by Behringwerke and Massachusetts General Hospital at the time it was filed. The file history of this application may be relevant to the instant application, including the decision in Appeal No. 2004-2109.

On October 4, 1990, Dr. Urdal of Immunex signed a paper acknowledging receipt in the United States of a BHK cell line from Behringwerke designated "TNFRFc A2," described as a BHK cell line producing TNFRFc fusion protein. **Exhibit K.** BHK cells are a hamster cell line.

On November 28, 1990, Behringwerke filed a patent application in Germany; and a corresponding U.S. application based on this German priority application issued as U.S. Patent No. 5,639,597 (Document No. A48 on the 1449 submitted on March 25, 2005). This patent discusses a "fusion protein TNFRFc."

On December 10, 1990, Dr. James Thomas, Director of Mammalian Cell Development at Immunex, wrote to Dr. Lauffer of Behringwerke to report binding affinity results of the protein expressed by the TNFRFc A2 cell line mentioned in Exhibit K, and to request a plasmid map and sequence information for the TNFRFc fusion protein. **Exhibit L.** Dr. Thomas asks: "would it be possible to obtain a complete plasmid map, including sequence information, for the TNFRFc molecule expressed in the TNFRFc A2 cell line."

On December 13, 1990, Dr. Lauffer replied to Dr. Thomas. **Exhibit M.** Dr. Lauffer states "the TNFRFc protein expressed by it still contains three extraneous amino acid residues (DPE) between the TNFR and Fc parts not belonging to either one." Dr. Lauffer also stated that a plasmid chart and restriction map were included with the letter and gave a brief description of how the plasmid was constructed.

2) Immunex Yeast Expression Efforts

A second, independent line of experimentation involved the construction by a second Immunex employee of vectors designed to express TNFR:Fc fusion proteins in yeast, as set forth in notebook pages attached as **Exhibit C**. Between May, 1990 and January, 1991, this second Immunex employee, independently of Berhringwerke, constructed vectors for expressing a TNFR:Fc protein in yeast. **Exhibit C**. A May 7, 1990 entry (lab notebook page 35) sets out the idea for the projected constructs, which were to be made using a murine IgG. The notebook page numbered 52 documents a ligation of a vector containing TNFR ("424") with a DNA fragment encoding a murine IgG Fc ("MuIgG FC") with two oligonucleotides designed such that the Fc fragment should be inserted in a particular orientation. *Escherichia coli* ("RRIs") colonies transformed with the ligation were screened by colony hybridization using one of the

oligonucleotides as a probe. Nucleic acids from nine positives were transformed into two yeast strains ("YNN-218" and "XU2181"). Supernatants were tested in a "bioassay" and the results "came back negative." On lab notebook pages numbered 62 and 63 are recorded PCR reactions designed to amplify a human cDNA encoding an IgG_1, which began on September 12, 1990. Orders for these oligos were placed on September 4, 1990, as seen on the previous unnumbered page. On the lab notebook page numbered 68, DNA from one *E. coli* transformant ("#8") is observed to have the correct structure and is sent to be sequenced. Construction of a fusion between human IgG-encoding sequences and human TNFR is begun on page 86 on November 18, 1990. On the previous unnumbered page, it is apparent that oligonucleotides were ordered on November 13 and 14, 1990. On the notebook page numbered 88, DNA from one E. coli colony was found to have the right structure and was transformed into yeast strain "YNN." On notebook page numbered 89 the notebook reports, "assay from Terry Davis returned no ligand bind [sic]."

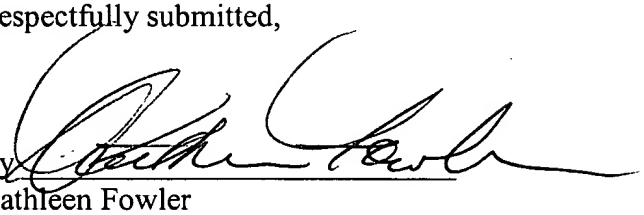
3) Beutler et al., University of Texas

A third line of experimentation was carried out at the University of Texas by Dr. Bruce Beutler, Karsten Peppel and David Crawford. This work led to U.S. Patent. No. 5,447,851 and U.S. Reexamination Certificate B1 5,447,851. U.S. Patent No. 5,447,851 was disclosed in the Information Disclosure statement filed on March 25, 2005 (Document No. A39 on the 1449 form). For the Examiner's convenience, Applicants submit a declaration of the inventors that was submitted in the course of the prosecution of U.S. 5,447,851 (**Exhibit J**), which is documented by 21 exhibits (Exhibits J1-J21). Exhibit J3 is dated before September 10, 1990.

Attached Table 1 is a chronological list of all documents submitted herewith.

If the Examiner would like further explanation or information, he is respectfully requested to contact the undersigned.

Respectfully submitted,



By _____
Kathleen Fowler
Registration No.: 40,611
Phone: 206-265-7847
Fax: 206-233-0644
Attorney for Applicant

TABLE 1

Exhibit	Description
Exhibit A	Memorandum dated October 27, 1989 from Dave Urdal of Immunex to Steve Gillis, Mike Kranda, and Pete Grassam of Immunex memorializing the discussion at an October 24, 1989 meeting in Seattle with Dr. Lauffer of Behringwerke.
Exhibit B	Correspondence dated February 26, 1990 documenting that Immunex sent and Behringwerke received a cDNA encoding the human TNF p75 receptor.
Exhibit C	Lab notebook pages of an Immunex employee dated May, 1990 through January, 1991.
Exhibit D	Correspondence dated May 21, 1990 in which Dr. Lauffer of Behringwerke discloses the sequence of a portion of a vector containing a genomic Fc-encoding sequence.
Exhibit E	A portion of Immunex internal meeting minutes dated June 25, 1990 in which it is announced that Behringwerke has sent a COS cell supernatant containing a TNFR:Fc protein.
Exhibit F	Lab notebook pages dated July 11, 1990 showing a TNF binding inhibition assay using the COS cell supernatant sent by Behringwerke.
Exhibit G	Letter dated July 20, 1990 from Dr. Deeley of Immunex to Dr. Lauffer of Behringwerke.
Exhibit H	Portion of internal Immunex meeting minutes dates July 23, 1990 in which the results documented in Exhibit F were reported.
Exhibit I	Correspondence dated August 8, 1990 from Drs. Seiler and Zetlmeiβl of Behringwerke to Dr. Gillis of Immunex.
Exhibit J (J1-J21)	Declaration of Bruce A. Beutler, Carsten Peppel, and David F. Crawford submitted during the prosecution of US 5,447,851 plus exhibits J1-J21, which were submitted with the declaration.
Exhibit K	Confirmation page dated October 4, 1990 acknowledging receipt by Immunex of a BHK cell line designated TNFRFc A2, producing TNFRFc fusion protein.
Exhibit L	Letter from Dr. Thomas of Immunex to Dr. Lauffer of Behringwerke dated December 10, 1990.
Exhibit M	Memo from Dr. Thomas to a number of Immunex scientists dated December 17, 1990 with attached letter from Dr. Lauffer of Behringwerke to Dr. Thomas of Immunex dated December 13, 1990.